EPIDEMIOLOGY OF AIDS DEFINING CONDITIONS IN GREECE

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SUMMARY

Objective: To examine the secular trends of all AIDS opportunistic infections to occur first (OIs) in Greece, by year, by gender and by mode of transmission.

Methods: The study included all AIDS defining conditions reported among Greek residents diagnosed with AIDS from 1981 to June 2003 and notified to the Hellenic Centre of Infectious Diseases Control. The analysis of trends in AIDS defining conditions in Greece has been performed only for the period 1993-2003.

Results: From 1981 to the first six months of 2003, 2,394 AIDS cases, 2,361 adults and 33 children, have been reported. HIV wasting syndrome was the most frequent OI to occur first followed by PCP pneumonia and Kaposi sarcoma. The frequency at which OIs occurred first varied by sex. Kaposi sarcoma was more frequent in males while tuberculosis and oesophageal candidiasis were more frequent in females. The frequency at which OIs occurred first varied also by exposure mode. Kaposi sarcoma was more frequent among men who have sex with men but that was not the case for the remaining transmission categories.

From 1993 to the first six months of 2003 a downward trend was noticed only for chronic simplex disease. Since the introduction of HAART, an increasing trend was noticed for CMV disease, recurrent pneumonia, oesophageal candidiasis, Burkitt and immunoblastic lymphoma.

Conclusion: Further epidemiological studies are needed to assess the OIs trends in coming years in order to plan prevention strategies and future medical care needs.

Key words: AIDS, opportunistic infections, trends

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INTRODUCTION

Opportunistic infections are the principal cause of severe illness and death among those infected with the HIV virus. It is also well known that they significantly influence the quality of life and the longevity as well.

AIDS-defining Opportunistic Infections (OIs) are the infections that are included in the European 1993 AIDS case definition (1).

We examined the temporal trends of all AIDS defining opportunistic infections in Greece, by year, by gender and by mode of transmission (2).

The study of OIs can provide information about effectiveness of preventive and therapeutic measures with regard to the occurrence of OIs. Furthermore, it helps to plan prevention strategies and future medical care needs and research.

METHODS

The study included all AIDS defining OIs reported among Greek residents diagnosed with AIDS from 1981 to June 2003 and notified to the Hellenic Centre of Infectious Diseases Control.

The way of notification of AIDS cases is briefly the following: When AIDS is diagnosed in an HIV infected person, a standard form is completed. Underreporting is estimated to be about 10%. Information is collected about demographic characteristics (age, gender, country of origin, place of residency), mode of HIV exposure, type and date of diagnosis of AIDS defining disease which may be more than one. It is pointed out that there is no personal identifying information.

The frequency at which AIDS-defining OIs occurred first was calculated by analyzing cases diagnosed with clinical AIDS from the beginning of epidemic through the first six months of 2003. The calculated incidence is for the first occurrence of each OI.

The analysis of trends in AIDS defining conditions in Greece has been performed only for the period 1993–2003.

RESULTS

From 1981 to the first six months of 2003, a total of 2,394 AIDS cases, 2,361 adults and 33 children, have been reported. Of the adult cases, 2,035 cases were males and 326 cases were females. At the time of diagnosis the majority of the adult cases ranged from 25 to 49 years old, while the peak was between 30 to 34 years old. Of the 33 children, 20 were males and 13 were females, while the children's age ranged from 0–12 years old.

Table 1 shows the frequency at which OIs occurred first in the adult AIDS population. HIV wasting syndrome was the most frequent AIDS defining OIs to occur first (18%), followed by *Pneumocystis carinii* pneumonia (PCP) (16%), Kaposi sarcoma (KS) (13%) and HIV encephalopathy (8%). In terms of the children, the most frequent OIs to occur first were *Pneumocystis carinii* pneumonia (12%), HIV encephalopathy (12%) and Cytomegalovirus (CMV) disease (12%).

The frequency at which OIs occurred first, varied by sex (Table 2, 3). HIV wasting syndrome and PCP pneumonia were the most frequent AIDS defining OIs to occur first in adult males and females as well. Pulmonary and extrapulmonary tuberculosis (TB) seems to occur more frequently in females than in males. Kaposi sarcoma was among the three most frequent OIs to occur first in

Table 1. *AIDS defining conditions in adult/adolescent men and women and children in Greece by 30/6/2003*

Indicative disease	Adults		Children	
	N=2361	%	N=33	%
HIV wasting	429	18	1	3
Pneumonocystis carinii pneumonia	372	16	4	12
Kaposi sarcoma	304	13	0	0
HIV dementia	185	8	4	12
Esophageal candidiasis	173	7	0	0
Pulmonary tuberculosis	161	7		
Brain toxoplasmosis	92	4	0	0
Chronic herpes simplex disease	84	4	0	0
CMV retinitis	67	3	1	3
Extrapulmonary tuberculosis	63	3	0	0
Progressive multifocal leucoencephalopathy	64	3	0	0
Lymphoma not specified	60	3	0	0
Recurrent pneumonia	63	3	0	0
CMV disease	58	2	4	12
Extrapulmonary cryptococcosis	51	2	0	0
Immunoblastic lymphoma	53	2	0	0
Chronic cryptosporidiasis	30	1	0	0
Mycobacterium avium complex	25	1	0	0
Recurrent *Salmonella septicaemia*	22	1	0	0
Pulmonary candidiasis	20	1	0	0
Burkittt's lymphoma	18	1	2	6
Other disseminated mycobacterium	10	0	0	0
Primary brain lymphoma	12	1	0	0
Invasive cervical cancer	3	0		
Chronic isosporiasis	2	0	0	0
Disseminated histoplasmosis	1	0	0	0
Disseminated coccidioidomycosis	0	0	0	0
Multiple or recurrent bacterial infections	0	0	1	3
Lymphoid interstitial pneumonia	0	0	1	3

males, but not in females. Esophageal candidiasis and chronic herpes simplex disease occurred more frequently in females than in males. Furthermore, while 59 cases of lymphoma not specified were reported in males, only one case was reported in females.

The frequency at which OIs occurred first, varied also by exposure mode (Table 2, 3). The OIs that occurred first most frequently in men who have sex with men (MSM) were KS, HIV wasting syndrome, PCP pneumonia and HIV dementia. However, while HIV wasting syndrome and PCP pneumonia were also among the OIs that most frequently occurred in males Injecting Drug Users (IDUs) and males exposed to HIV through heterosexual contact, this was not the case for KS and HIV dementia. In addition, no case of Non-Hodgkin Lymphomas (NHL) as AIDS defining OIs to occur first was reported among male IDUs, while in the remaining transmission categories, immunoblastic lymphoma and lymphoma not specified were presented quite often. HIV wasting syndrome was the most frequent AIDS defining OI to occur first in IDUs females and in females exposed to HIV through heterosexual contact. However, recurrent pneumonia was the second most frequent OI to occur in IDUs females, while in females exposed to HIV through heterosexual contact, PCP pneumonia was the second OI to occur first. It is pointed out that no case of NHL as AIDS defining OI to occur first was reported in females IDUs as well.

From 1993 to the first six months of 2003 an upward trend was noticed for *Candida esophagitis*, extrapulmonary tuberculosis, recurrent pneumonia, Burkitt lymphoma and immunoblastic lymphoma, while a downward trend was noticed only for chronic herpes simplex disease. For the rest of the OIs no significant trend was recorded during that period.

Regarding the impact of HAART on the incidence of AIDS defining conditions in Greece, an increasing trend for *Candida esophagitis*, Cytomegalovirus (CMV) disease, recurrent pneumonia, Burkitt and immunoblastic lymphoma was observed since the introduction of Highly Active Antiretroviral Treatment (HAART)

Table 2. *Percentage of males in whom a given OI occurred first, by disease and human immunodeficiency virus (HIV) exposure mode (in %)*

Indicative disease	Total	Men who have sex with men	Injection drug users	Men exposed to HIV through heterosexual contact
HIV wasting	17	17.13	30.99	19.35
Pneumonocystis carinii pneumonia	16	16.84	12.68	13.36
Kaposi sarcoma	14	17.87	2.82	9.68
HIV dementia	8	7.43	15.49	4.61
Esophageal candidiasis	7	6.91	9.86	10.14
Pulmonary tuberculosis	6	5.66	9.86	9.22
Brain toxoplasmosis	4	3.97	5.63	2.76
Chronic herpes simplex disease	3	3.75	5.63	
CMV retinitis	3	3.24	4.23	1.38
Progressive multifocal leucoencephalopathy	3	2.65	4.23	3.23
Lymphoma not specified	3	2.50	0	2.3
Recurrent pneumonia	3	2.06	2.82	3.23
Extrapulmonary tuberculosis	2	1.84	1.41	4.15
CMV disease	2	3.09	1.41	1.38
Extrapulmonary cryptococcosis	2	1.84	0	0.92
Immunoblastic lymphoma	2	1.99		4.15
Chronic cryptosporidiosis	1	1.03	1.41	2.76
Pulmonary candidiasis	1	0.81	1.41	0
Burkitt's lymphoma	1	0.59		1.38
Mycobacterium avium complex	1	1.62	0	0
Other disseminated mycobacterium	0	0.51	0	0.46
Disseminated coccidioidomycosis	0	0	0	0
Disseminated histoplasmosis	0	0.07	0	0
Chronic isosporiasis	0	0.15	0	0
Recurrent *Salmonella septicemia*	0	0.74	0	1.84
Primary brain lymphoma	0	0.59		0.46
Multiple or recurrent bacterial infections	0	0	0	0
Lymphoid interstitial pneumonia	0	0	0	0

in 1996. No significant trend was observed in the rest of the OIs in the meta-HAART era.

DISCUSSION

Since the onset of epidemic in the first six months of 2003, the most common AIDS defining OI to occur first was HIV wasting syndrome. It seems that worldwide, especially in the south-west Europe (3), HIV wasting syndrome is one of the most frequent OIs related to AIDS (4,5), even in the HAART era (4). It is noteworthy that HIV wasting syndrome is the third among the six AIDS-defining conditions with the highest percentages of the first time acquisition in the last six months of life in AIDS patients (4). *Pneumocystis carinii* pneumonia is among the most frequent AIDS defining OIs to occur first, regardless of sex, and mode of exposure (6). The introduction of HAART had a substantial impact on the incidence of *Pneumocystis carinii* pneumonia mainly due to induced immune reconstitution (7). However, late diagnosis of HIV status, failure to receive primary PCP prophylaxis (8, 9, 10) and poor adherence to PCP prophylaxis (11, 12) are the main reasons for the high incidence of PCP pneumonia even in the HAART era (8). It does appear that the incidence of Kaposi sarcoma in persons receiving combination antiretroviral therapy has fallen dramatically (13–18) but it seems to remain among the most frequent AIDS OIs to occur first. The main reason that HIV encephalopathy remains one of the most common AIDS defining conditions even after the introduction of HAART, is that antiretroviral combination therapy seems to have lesser impact on HIV dementia than on the other AIDS defining illnesses (19, 20, 21). A marked reduction in incidence of esophageal candidiasis as OI was recorded (22, 23) especially after HAART initiation, but it still remains one of the most common AIDS defining conditions. On the other hand, coinfection with tuberculosis and HIV continues

Table 3. *Percentage of females in whom a given OI occurred first, by disease and human immunodeficiency virus (HIV) exposure mode (in %)*

Indicative disease	Total	Injecting drug users	Females exposed to HIV through heterosexual contact
HIV wasting	23	36.36	20.33
Pneumonocystis carinii pneumonia	16	4.55	16.18
Pulmonary tuberculosis	10	9.09	12.03
HIV dementia	9	9.09	8.71
Esophageal candidiasis	8	9.09	7.47
Brain toxoplasmosis	6		7.05
Chronic herpes simplex disease	4	4.55	4.56
Extrapulmonary tuberculosis	4	4.55	4.98
Recurrent pneumonia	4	13.64	3.32
Kaposi sarcoma	3	9.09	3.32
CMV retinitis	3	0	4.15
Extrapulmonary cryptococcosis	3	0	4.98
Immunoblastic lymphoma	3	0	3.32
Progressive multifocal leucoencephalopathy	2	0	2.07
CMV disease	2	0	2.90
Chronic cryptosporidiosis	2	0	1.66
Pulmonary candidiasis	2	0	2.07
Mycobacterium avium complex	1	0	1.24
Recurrent *Salmonella septicemia*	1	0	0.83
Burkitt's lymphoma	1	0	0.41
Primary brain lymphoma	1	0	1.24
Invasive cervical cancer	1	0	1.24
Other disseminated mycobacterium	0	0	0.41
Disseminated coccidioidomycosis	0	0	0
Disseminated histoplasmosis	0	0	0
Chronic isosporiasis	0	0	0
Lymphoma not specified	0	0	0
Multiple or recurrent bacterial infections	0	0	0
Lymphoid interstitial pneumonia	0	0	0

to be a huge problem in both the developing and developed world. Immigrants and residents of group facilities, such as prisons and shelters, are especially involved. Pulmonary tuberculosis was added to the WHO AIDS case definition as an AIDS defining disease in 1993, whereas extrapulmonary tuberculosis was AIDS defining condition before 1987. The region of origin is the strongest risk factor for pulmonary and extrapulmonary tuberculosis (24, 25, 26). Tuberculosis is more common in Southwest Europe than in North Europe, so in Greece it is one of the most common AIDS defining OIs. It is pointed out that while *Mycobacterium Avium* Complex (MAC) was more than twice as common as TB in the pre-HAART era, at least in the European region, TB has now become the most common mycobacteriosis (25). After the initiation of HAART and toxoplasmosis prophylaxis, brain toxoplasmosis as AIDS defining condition is less frequent (27, 28, 29) but not eliminated. This is probably due to the poor adherence to HAART and toxoplasmosis prophylaxis. It is well known that non. Hodgkin lymphoma incidence, especially that of immunoblastic and Burkitt lymphoma, decreased less than Kaposi sarcoma, since the widespread use of potent anti-retroviral therapy (14,16, 30). Our study's evidence enhances the above documents.

Several reports have been published concerning the gender differences in reported AIDS defining conditions. Esophageal candidiasis and chronic herpes simplex disease were most frequent in women than in men in a study of Fleming et al. (6). Cadman et al. assume that the vaginal colonization with Candida in women is responsible for the higher rates of esophageal candidiasis (31). Higher rates of chronic herpes simplex disease may occur in women because the disease is more common in females IDUs than in males IDUs (32). In our study a slight increase of *Candida esophagitis* and chronic herpes simplex disease in females was observed. Furthermore, tuberculosis, pulmonary and extrapulmonary, was most frequent in women than in men.

Gender differentials in social, economic roles and activities may lead to differential exposure to tuberculosis bacilli. In areas where women's health is worse than men's, women's risk of disease may be increased (33). This is the case especially for the great number of immigrants living in Greece in recent years. Rates of KS were higher in males than in females because it is associated with sexual transmission and a larger proportion of men than women have sexual HIV risks (9).

Different frequencies at which OIs occur first have been observed by mode of exposure to HIV. Kaposi sarcoma is observed almost exclusively in men who have sex with men since the transmission of HHV8 (34) is associated with unsafe sexual practices more often noticed in MSM. Tuberculosis in the other hand is most frequent in IDUs than in the other transmission categories because of their life-style. Recurrent pneumonia is also more frequent in IDUs population (35).

In Greece an upward trend has been noticed for *Candida esophagitis*, extrapulmonary TB, recurrent pneumonia, Burkitt and immunoblastic lymphoma, during 1993–2003. There are not published data concerning the incidence of AIDS defining conditions for the same time period. Several reports though have been published in terms of AIDS defining conditions surveillance mainly up to 1996 from USA and Europe as well. In these reports the results are quite conflicting. For example, un upward trend was noticed through the years 1992–1996 in USA for esophageal candidiasis, while a downward trend was noticed in Italy from 1982–1996 (22). Furthermore an upward trend for TB has been observed in Europe (22) but a downward trend was described in USA (9). In a low HIV and tuberculosis prevalence area such as the Czech Republic, the risk of AIDS patients to contact classical tuberculosis is considered low (36, 37). The fact that recurrent pneumonia and pulmonary tuberculosis were added to the AIDS surveillance case definition in 1993 may have had some impact on the pattern of those OIs. As for Burkitt and immunoblastic lymphoma, a downward trend has been recorded in Italy while none trend has been recorded in USA. Chronic herpes simplex disease is the only OI that exhibits a decreasing trend in Greece during 1993–2003, while the rest of the OIs have no significant trend. Evidence of decreasing trend in chronic herpes simplex disease was presented from Italy and USA surveillance programs of AIDS defining conditions.

In the 39th Annual Meeting of the Infectious Disease Society of America according to the report from the Centers for Disease Control and Prevention (CDC)'s Adult-Adolescent Spectrum of Disease Project (ASD) (38), the incidence of AIDS-defining opportunistic infections is no longer declining but appears to be leveling off. Between 1995 and 1999, investigators collected data on 20,455 patients in 11 cities. The data from this cohort revealed that from 1998 to 1999 there was no reduction in the incidence of any OIs for females; for males, only the incidence of cerebral toxoplasmosis and CMV retinitis declined. By 1998, this population of patients may have attained maximum benefit from HAART. The development of retroviral resistance adverse drug effects and poor adherence may limit the potential for this cohort to attain further benefit.

It is therefore of great importance to watch OIs trends in coming years to determine whether the incidence of OIs remains stable or even increases, as patients run out of antiretroviral regimens that are effective and tolerable.

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